NEW ZEALAND DATA SHEET

1 PRODUCT NAME

DUORESP SPIROMAX 200/6

Budesonide/formoterol fumarate dihydrate Dry Powder Inhaler (200 µg/6 µg per inhalation)

DUORESP SPIROMAX 400/12

Budesonide/formoterol fumarate dihydrate Dry Powder Inhaler (400 µg/12 µg per inhalation)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredients

Budesonide

Formoterol fumarate dihydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

DUORESP SPIROMAX is a multidose inspiratory flow driven, dry powder inhaler. The inhaler is made of plastic parts.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ASTHMA
DUORESP SPIROMAX is indicated in the treatment of asthma to achieve overall asthma control, including the prevention and relief of symptoms as well as the reduction of the risk of exacerbations.

DUORESP SPIROMAX is suitable for any asthma severity, where the use of inhaled corticosteroids is appropriate (See Section 4.2 Dose and Method of Administration).

COPD
DUORESP SPIROMAX is indicated in the regular treatment of adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) [$FEV_1 \leq 50\%$ of predicted normal], with frequent symptoms despite $beta_2$-agonist use and a history of exacerbations.

DUORESP should not be used for the initiation of bronchodilator therapy in COPD.

4.2 Dose and method of administration

The dosage of DUORESP SPIROMAX should be individualised according to disease severity.

ASTHMA

DUORESP can be used according to different treatment approaches:

A. Anti-inflammatory reliever therapy (patients with mild disease).

B. Anti-inflammatory reliever plus maintenance therapy

As an alternative, DUORESP SPIROMAX can be used in a fixed dose therapy:

C. Maintenance therapy (fixed dose)

If patients take DUORESP as a maintenance therapy, they should be instructed to take the maintenance dose of DUORESP SPIROMAX even when asymptomatic for optimal benefit.

Anti-inflammatory reliever therapy (patients with mild disease):

DUORESP SPIROMAX 200/6 is taken as needed for the relief of asthma symptoms when they occur, and to prevent allergen induced bronchoconstriction or exercise induced bronchoconstriction (or to prevent symptoms in those circumstances recognised by the patient to precipitate an asthma attack). The formoterol component in DUORESP SPIROMAX provides fast onset of effect (within 1-3 minutes) with long-acting (at least 12 hours after a single dose) bronchodilation in reversible airways obstruction. Patients should be advised to always have DUORESP SPIROMAX 200/6 available for relief of symptoms.

Clinical studies have demonstrated that anti-inflammatory reliever therapy provides significant reductions in severe exacerbations and was statistically superior on daily asthma symptom control compared to a short-acting beta-2 agonist therapy alone (see section 5.1 Pharmacodynamic properties).

Recommended doses:

Physicians should discuss allergen exposure and exercise patterns with the patients and take these into consideration when recommending the dose frequency.

Adults and Adolescents (12 years and older):

Patients should take 1 inhalation of DUORESP SPIROMAX 200/6 as needed in response to symptoms and for the prevention of allergen induced bronchoconstriction or exercise induced bronchoconstriction to control asthma. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion.

A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. Patients using more than 8 inhalations daily should be reassessed for alternative explanations of persisting symptoms.

Anti-inflammatory reliever plus maintenance therapy

When maintenance treatment with a combination of inhaled corticosteroid and long-acting beta-2-agonist (LABA) is required, DUORESP is taken as anti-inflammatory reliever therapy and in addition, patients take a daily maintenance dose of DUORESP SPIROMAX. The as needed inhalations provide both rapid relief of symptoms and improved overall asthma control. Patients should be advised to have DUORESP SPIROMAX available for relief of symptoms at all times. A separate inhaler for relief of symptoms is not necessary.

Clinical studies have demonstrated that 200/6 anti-inflammatory reliever plus maintenance therapy provides clinically meaningful reductions in severe exacerbations while maintaining

symptom control, compared to maintenance therapy with a separate short-acting bronchodilator (see section 5.1 Pharmacodynamic properties).

The maintenance dose should be titrated to the lowest dose at which effective control of asthma is maintained.

Recommended doses:

Physicians should discuss allergen exposure and exercise patterns with the patients and take these into consideration when recommending the dose frequency.

Adults and Adolescents (12 years and older):

Patients should take 1 inhalation of DUORESP SPIROMAX 200/6 as needed in response to symptoms to control asthma. Patients on DUORESP SPIROMAX 200/6 can also take 1 inhalation for the prevention of allergen induced bronchoconstriction or EIB. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion.

Patients also take the recommended maintenance dose, which is 2 inhalations of DUORESP SPIROMAX 200/6 per day, given either as one inhalation in the morning and one in the evening or as 2 inhalations in either the morning or the evening. For some patients, a maintenance dose of 2 inhalations twice daily may be appropriate.

A total daily dose of more than 8 inhalations is not normally needed, however a total daily dose of up to 12 inhalations can be used temporarily. If the patient experiences deteriorating symptoms after taking the appropriate maintenance therapy and additional as needed inhalations, the patient should be reassessed for alternative explanations of persisting symptoms.

Note - DUORESP SPIROMAX 400/12 should not be used for the anti-inflammatory reliever plus maintenance therapy regimen.

Maintenance therapy (fixed dose):

When maintenance treatment with a combination of inhaled corticosteroid and long-acting beta-2-agonist is required, DUORESP is taken as a fixed daily dose treatment, with a separate short-acting bronchodilator for relief of symptoms. Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times.

Increasing use of a separate rapid acting bronchodilator indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy.

When control has been achieved, the dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

Adults and Adolescents (12 years and older):

DUORESP 200/6: 1-2 inhalations once or twice daily

Maximum daily maintenance dose: 4 inhalations. (2 inhalations twice daily).

During worsening of asthma the dose of DUORESP 200/6 may temporarily be increased to a maximum of 4 inhalations twice daily in adults.

DUORESP 400/12: 1 inhalation once or twice daily

Maximum daily maintenance dose: 2 inhalations (1 inhalation twice daily).

During worsening of asthma the dose of DUORESP 400/12 may temporarily be increased to a maximum of 2 inhalations twice daily in adults.

COPD

Adults (40 years and older):

DUORESP 200/6: 2 inhalations twice daily

Maximum daily maintenance dose: 4 inhalations

DUORESP 400/12: 1 inhalation twice daily

Maximum daily maintenance dose: 2 inhalations.

Special Populations

There is no special dosing requirement in elderly patients.

There are no data available for use of budesonide and formoterol in patients with hepatic or renal impairment. As budesonide and formoterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver disease.

Instruction for correct use of SPIROMAX

Spiromax is a reservoir type, breath actuated, inspiratory flow-driven inhaler, which means that the active substances are delivered into the airways when the patient inhales through the mouthpiece. Moderate and severe asthmatic patients were shown to be able to generate a sufficient inspiratory flow rate for Spiromax to deliver the therapeutic dose (refer **CLINICAL TRIALS** *Peak Inspiratory Flow Rate through the Spiromax Device*).

DUORESP SPIROMAX should be used correctly in order to achieve effective treatment. Patients should be advised to read the patient information leaflet carefully and follow the instructions for use as detailed in the leaflet.

The use of DUORESP SPIROMAX follows three steps: open, breathe and close which are outlined below.

Open: Hold the SPIROMAX with the mouthpiece cover at the bottom and open the mouthpiece cover by folding it down until it is fully opened when one click is heard.

Breathe: Place the mouthpiece between the teeth with the lips closed around the mouthpiece. Do not bite the mouthpiece of the inhaler. Inhale forcefully and deeply through the mouthpiece. Remove the Spiromax from the mouth and hold the breath for 10 seconds, or as long as comfortable.

Close: Breathe out gently and close the mouthpiece cover.

It is important to advise patients not to shake the inhaler before use and to not exhale through the Spiromax. Patients should not block the air vents during preparation for the "Breathe" step.

Patients should rinse their mouth with water after inhaling.

The patient may notice a taste when using DUORESP SPIROMAX due to the lactose excipient.

4.3 Contraindications

Hypersensitivity to budesonide, formoterol or to lactose.

4.4 Special warnings and precautions for use

For treatment of severe exacerbations, a combination product of inhaled corticosteroid and long-acting beta-2-agonist alone is not sufficient.

Dosing and Discontinuation

The management of asthma should normally follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.

The lowest effective dose of DUORESP SPIROMAX should be used.

Patients should be reminded to take their DUORESP SPIROMAX maintenance dose as prescribed, even when asymptomatic. They should also be advised to have their rescue inhaler available at all times, either DUORESP SPIROMAX (for asthma patients on t anti-inflammatory reliever therapy) or a separate short-acting bronchodilator (for asthma patients using DUORESP SPIROMAX as maintenance therapy only and for COPD patients).

In patients using the anti-inflammatory reliever(asthma therapies A and B) , the reliever inhalations of DUORESP SPIROMAX should be taken in response to asthma symptoms for the prevention of allergen- or exercise- induced bronchoconstriction to control asthma.

If the patient finds the treatment ineffective or exceeds the highest recommended dose of DUORESP SPIROMAX, the patient should be reviewed by a physician.

Once asthma symptoms are controlled, consideration may be given to stepping down treatment with DUORESP SPIROMAX. Regular review of patients as treatment is stepped down is important.

It is recommended that the maintenance dose is tapered when long-term treatment with DUORESP SPIROMAX is to be discontinued and the dosing should not be stopped abruptly. Complete withdrawal of inhaled corticosteroids should not be considered unless it is temporarily required to confirm the diagnosis of asthma.

Deterioration of Asthma Control

Increasing use of DUORESP SPIROMAX for reliever therapy or short-acting bronchodilators to relieve symptoms indicates deterioration of control.

Sudden and progressive deterioration in control of asthma or COPD is potentially life threatening and the patient should undergo urgent medical assessment. In this situation, consideration should be given to the need for increased therapy with corticosteroids, e.g. a course of oral corticosteroids, or antibiotic treatment if an infection is present. Patients should

be advised to seek medical attention if they find the treatment ineffective or they have exceeded the prescribed dose of DUORESP SPIROMAX.

Asthma Exacerbations

Serious asthma-related adverse events and exacerbations may occur during treatment with DUORESP SPIROMAX. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen during treatment with DUORESP SPIROMAX.

Patients should be advised to seek medical attention if they experience deteriorating symptoms after taking the appropriate maintenance therapy and additional as needed inhalations if using it as an anti-inflammatory reliever.

Potential Systemic Effects of Inhaled Corticosteriods

DUORESP SPIROMAX contains an inhaled corticosteroid (budesonide).

DUORESP SPIROMAX should not be used to initiate treatment with inhaled corticosteroids in patients being transferred from oral steroids.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. However, these effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, and glaucoma, blurred vision and more rarely a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained.

Increased susceptibility to infections and impairment of the ability to adapt to stress may also occur.

Effects are probably dependent on dose, exposure time, concomitant and previous steroid exposure and individual sensitivity. Therefore it is important that the patient is reviewed regularly and the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained.

HPA Axis Suppression and Adrenal Insufficiency

Dose-dependent HPA axis suppression (as indicated by 24 hour urinary and/or plasma cortisol AUC) has been observed with inhaled budesonide, although the physiological circadian rhythms of plasma cortisol were preserved. This indicates that the HPA axis suppression represents a physiological adaptation in response to inhaled budesonide, not necessarily adrenal insufficiency. The lowest dose that results in clinically relevant adrenal insufficiency has not been established. Very rare cases of clinically relevant adrenal dysfunction have been reported in patients using inhaled budesonide at recommended doses.

Clinically important disturbances of the HPA axis and/or adrenal insufficiency induced by severe stress (eg trauma, surgery, infection in particular gastroenteritis or other conditions associated with severe electrolyte loss) may be related to inhaled budesonide in specific patient populations. These are patients with prolonged treatment at the highest recommended dose of DUORESP and patients administered concomitant CYP3A4-inhibitors (see 4.5

INTERACTIONS). Monitoring for signs of adrenal dysfunction is advisable in these patient groups. For these patients additional systemic glucocorticosteroid cover should be considered during periods of stress, a severe asthma attack or elective surgery.

Transfer from Oral Therapy

Particular care is needed in patients transferring from oral steroids, since they may remain at risk of impaired adrenal function for a considerable time. Patients who have required high-dose emergency corticosteroid therapy or prolonged treatment at the highest recommended dose of inhaled corticosteroids may also be at risk. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Care should be taken when commencing DUORESP SPIROMAX treatment, particularly if there is any reason to suspect that adrenal function is impaired from previous systemic steroid therapy.

A fixed -dose combination of budesonide and formoterol fumarate dihydrate should be administered with caution in patients with phaeochromocytoma.

Bone Density

Whilst corticosteroids may have an effect on bone mass at high doses, studies with budesonide treatment in adults at recommended doses, have not demonstrated any significant effect on bone mineral density. No information regarding the effect of DUORESP SPIROMAX at higher doses is available.

Potential effects on bone density should be considered, particularly in patients on high doses for prolonged periods that have co-existing risk factors for osteoporosis.

Bone mineral density measurements in children should be interpreted with caution as an increase in bone area in growing children may reflect an increase in bone volume. In three large medium to long term (12 months - 6 years) studies in children (5-16 years), no effects on bone mineral density were observed after treatment with budesonide (189 - 1322µg/day) compared to nedocromil, placebo or age matched controls. However, in a randomised 18 month study (n=176; 5-10 years), bone mineral density was significantly decreased by 0.11 g/cm^2 (p=0.023) in the group treated with inhaled budesonide compared with the group treated with inhaled disodium cromoglycate. The dose of budesonide was 400 µg twice-daily for 1 month, 200 µg twice-daily for 5 months and 100 µg twice-daily for 12 months and the dose of disodium cromoglycate 10 mg three times daily. The clinical significance of this result remains uncertain.

Growth

Long term studies suggest that children and adolescents treated with inhaled budesonide ultimately achieve their adult target height. However an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment.

It is recommended that the height of children and adolescents receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid to the lowest dose at which effective control of asthma is maintained, if possible.

Physicians should carefully weigh the benefits of the corticosteroid therapy against the possible risk of growth suppression.

Visual disturbances

Visual disturbances may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Oropharyngeal Candida Infection

Candida infection in the oropharynx has been reported due to drug deposition in association with inhalation therapy. To minimise the risk of oropharyngeal candida infection (see section 4.8 Undesirable Effects), the patient should be instructed to rinse their mouth out with water after inhaling the maintenance dose. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations. Oropharyngeal candida infection usually responds to topical anti-fungal treatment without the need to discontinue the inhaled corticosteroids.

Paradoxial Bronchospasm

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing and shortness of breath after dosing. If the patient experiences paradoxical bronchospasm DUORESP SPIROMAX should be discontinued immediately, the patient should be assessed, and an alternative therapy instituted if necessary. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway.

Patients with Other Medical Conditions

Infections/Tuberculosis

Signs of existing infection may be masked by the use of high doses of glucocorticosteroids and new infections may appear during their use.

As with all inhaled medication containing corticosteroids, DUORESP SPIROMAX should be administered with caution in patients with active or quiescent pulmonary tuberculosis or fungal, bacterial or viral infections of the respiratory system.

Sensitivity to Sympathomimetic amines

In patients with increased susceptibility to sympathomimetic amines (e.g. inadequately controlled hyperthyroidism), formoterol should be used with caution.

Thyrotoxicosis

DUORESP SPIROMAX should be administered with caution in patients with thyrotoxicosis.

Cardiovascular Disorders

Beta$_2$-agonists have an arrhythmogenic potential that must be considered before commencing treatment for bronchospasm. Cardiovascular effects, such as increases in systolic blood pressure and heart rate, may occasionally be seen with all sympathomimetic medicines, especially at higher than therapeutic doses.

The effects of formoterol in acute as well as chronic toxicity studies were seen mainly on the cardiovascular system and consisted of hyperaemia, tachycardia, arrhythmias and myocardial lesions. These are known pharmacological manifestations seen after administration of high doses of beta-$_2$-adrenoceptor agonists.

Patients with pre-existing cardiovascular conditions may be at greater risk of developing adverse cardiovascular effects following administration of beta-$_2$-adrenoreceptor agonists.

Caution is advised when formoterol is administered to patients with severe cardiovascular disorders such as ischaemic heart disease, tachyarrhythmias hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or severe heart failure.

QTc-interval Prolongation

Caution should be observed when treating patients with prolongation of the QTc-interval. formoterol itself may induce prolongation of the QTc-interval.

Hypokalaemia

DUORESP SPIROMAX should be administered with caution in patients predisposed to low levels of serum potassium.

High doses of beta-2 agonists can lower serum potassium by inducing a redistribution of potassium from the extracellular to the intracellular compartment, via stimulation of Na^+/K^+-ATPase in muscle cells.

Concomitant treatment of beta-2 adrenoceptor agonists with drugs which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine-derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the beta-2 adrenoceptor agonist. Potentially serious hypokalaemia may result.

Particular caution is advised in unstable or acute severe asthma as the associated risk may be augmented by hypoxia. The hypokalaemic effect may be potentiated by concomitant treatments (see 4.5 INTERACTIONS). Patients receiving digoxin are particularly sensitive to hypokalaemia. Serum potassium levels should therefore be monitored in such situations.

Diabetes Mellitus

DUORESP SPIROMAX should be administered with caution in patients with diabetes mellitus.

Due to the blood-glucose increasing effects of beta$_2$-stimulants extra blood glucose controls are initially recommended when diabetic patients are commenced on formoterol.

Lactose Intolerance

DUORESP SPIROMAX contains lactose. This amount does not normally cause problems in lactose intolerant people. The excipient lactose contains small amounts of milk proteins which may cause allergic reactions.

Pneumonia in COPD Patients

Clinical studies and meta-analyses indicate that treatment of COPD with inhaled corticosteroids may lead to an increased risk of pneumonia.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap.

Drug Interaction Potential

Concomitant treatment with ritonavir, itraconazole, ketoconazole or other potent CYP3A4 inhibitors should be avoided (see section 4.5). If this is not possible, the time interval between administration of the interacting drugs should be as long as possible.

In patients using potent CYP3A4 inhibitors, DUORESP as an anti-inflammatory reliever is not recommended.

In vivo studies have shown that oral administration of ketoconazole or itraconazole (known inhibitors of CYP3A activity in the liver and in the internal mucosa, also see section 4.5) may cause an increase in the systemic exposure to budesonide, and consequently lead to systemic adverse reactions, such as Cushing′s Syndrome. This is of limited importance for short-term (1-2 weeks) treatment, but should be taken into consideration during long-term treatment.

4.5 Interaction with other medicines and other forms of interaction

Budesonide and formoterol have not been observed to interact with any other medicines used in the treatment of asthma.

Formoterol

Beta-receptor blocking agents:

Beta-receptor blocking agents (including eye drops), especially those that are non-selective, may partially or totally inhibit the effect of beta-2-agonists, such as formoterol. These medicines may also increase airway resistance, therefore the use of these medicines in asthma patients is not recommended.

Other sympathomimetic agents:

Other beta-adrenergic stimulants or sympathomimetic amines such as ephedrine and anticholinergics should not be given concomitantly with formoterol, since the bronchodilating effects will be cumulative. Patients who have already received large doses of sympathomimetic amines should not be given formoterol.

Xanthine derivatives, mineralcorticosteroids and diuretics:

Hypokalaemia may result from beta-2-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, mineralocorticosteroids, and diuretics, such as thiazides and loop diuretics (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - HYPOKALAEMIA section).

Hypokaelaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

Monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines and antihistamines:

The adverse cardiovascular effects of formoterol may be exacerbated by concurrent administration of medicines associated with QT interval prolongation. For this reason caution is advised when formoterol is administered to patients already taking monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines or antihistamines associated with QT interval prolongation (e.g. terfenadine, astemizole) as these can prolong the QTc-interval and increase the risk of cardiovascular effects such as ventricular arrhythmias.

Concomitant treatment with monoamine oxidase inhibitors, including agents with similar properties such as furazolidone and procarbazine, may precipitate hypertensive reactions.

L-Dopa, L-thyroxine, oxytocin and alcohol:

L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta-2 sympathomimetics.

Halogenated hydrocarbons:

There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

Budesonide

CYP3A4 Inhibitors

The metabolism of budesonide is primarily mediated by CYP3A4. Inhibitors of this enzyme, e.g. ketoconazole and itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone, ritonavir and HIV protease inhibitors, can therefore increase plasma levels and thus systemic exposure to budesonide (see WARNINGS and PRECAUTIONS). The concomitant use of these medicines should be avoided unless the benefit outweighs the increased risk of systemic side effects. If this is not possible, the time interval between administration of the interacting drugs should be as long as possible.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

In patients using potent CYP3A4 inhibitors, the anti-inflammatory reliever therapy is not recommended.

At recommended doses, cimetidine has a slight but clinically insignificant effect and omeprazole has no effect on the pharmacokinetics of oral budesonide.

In vivo studies have shown that oral administration of ketoconazole or itraconazole (known inhibitors of CYP3A activity in the liver and in the internal mucosa, also see 4.5 INTERACTIONS) may cause an increase in the systemic exposure to budesonide, and consequently lead to systemic adverse reactions, such as Cushing's Syndrome. This is of limited importance for short-term (1-2 weeks) treatment, but should be taken into consideration during long-term treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

DUORESP SPIROMAX should only be used in pregnancy if the potential benefits outweigh the potential risks to the foetus. Only after special consideration should DUORESP SPIROMAX be used during the first 3 months and shortly before delivery.

DUORESP SPIROMAX should be used during labour only if the potential benefit justifies the potential risk.

For DUORESP SPIROMAX or for concomitant treatment with budesonide and formoterol, no clinical data on exposed pregnancies are available. Data from an embryo-foetal development study in the rat, showed no evidence of any additional effect from the combination.

There are no adequate data from use of formoterol in pregnant women. In animal studies formoterol has caused adverse effects in reproduction studies at very high systemic exposure levels (see PHARMACOLOGICAL PROPERTIES – 5.3 Pre-Clinical Safety Data).

Data in more than 17000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide.

Lactation

Administration of DUORESP SPIROMAX to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Budesonide is excreted in breast milk; however, due to the relatively low doses used via the inhaled route, the amount of drug present in the breast milk, if any, is likely to be low. Consequently, no adverse effects due to budesonide are anticipated in breast-fed children whose mothers are receiving therapeutic doses of DUORESP.

It is not known whether formoterol passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk.

4.7 Effects on ability to drive and use machines

DUORESP SPIROMAX is not expected to adversely affect the ability to drive or use machines. However, adverse effects of this medicine include dizziness and blurred vision/visual disturbances which could affect the ability to drive or use machines (see Section 4.8 Undesirable effects).

4.8 Undesirable effects

Since DUORESP SPIROMAX contains both budesonide and formoterol, the same pattern of undesirable effects as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side effects of beta2-agonist therapy, such as tremor and palpitations. These tend to be mild and disappear within a few days of treatment.

Adverse events which have been associated with budesonide and / or formoterol are given below listed by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1000) and very rare (< 1/10 000).

Table 1 Adverse Drug Reactions by frequency and system organ class (SOC)

Frequency	System Organ Class	Reaction
Common	Cardiac disorders	Palpitations
1 to 10%	Infections and infestations	Candida infections in the oropharynx Pneumonia (in COPD patients)
	Nervous system disorders	Headache, tremor
	Respiratory; thoracic & mediastinal disorders	Mild irritation in the throat, coughing, hoarseness
Uncommon	Cardiac disorders	Tachycardia
0.1 to 1%	Eye disorders	Blurred vision
	Gastrointestinal disorders	Nausea, diarrhoea
	Metabolism and nutrition disorders	Weight gain
	Musculoskeletal & connective tissue disorders	Muscle cramps
	Nervous system disorders	Dizziness, bad taste, thirst, tiredness
	Psychiatric disorders	Agitation, restlessness, nervousness, anxiety, sleep disturbances
	Skin and subcutaneous disorders	Bruises
Rare	Cardiac disorders	Cardiac arrhythmias eg atrial fibrillation, supraventricular tachycardia, extrasystoles
0.01 to 0.1%	Immune system disorders	Immediate and delayed hypersensitivity reactions e.g. dermatitis, exanthema, urticaria, pruritis, angioedema and anaphylactic reaction
	Respiratory, thoracic & mediastinal disorders	Bronchospasm
	Skin & subcutaneous tissue disorders	Skin bruising
	Metabolism & nutrition disorders	Hypokalaemia
Very Rare	Cardiac disorders	Angina pectoris, Prolongation of QTc-interval
< 0.01%	Eye disorders	Cataract and glaucoma
	Endocrine disorders	Signs or symptoms of systemic glucocorticosteroid effects, e.g. Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral
	Eye Disorders	Cataract and Glaucoma
	Metabolism & nutrition disorders	Hyperglycaemia
	Psychiatric disorders	Anxiety, depression, behavioural disturbances

Frequency	System Organ Class	Reaction
	Respiratory, thoracic & mediastinal disorders	Paradoxical bronchospasm
	Vascular disorders	Variations in blood pressure
Not Known	Eye Disorders	Central serous retinopathy

Treatment with beta-2 adrenoceptor agonists may also result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Formoterol

An overdose of formoterol would likely lead to effects that are typical for beta-2-adrenergic agonists: tremor, headache, palpitations, and tachycardia. Hypotension, metabolic acidosis, prolonged QTc-interval, arrhythmia, nausea, vomiting, hypokalaemia and hyperglycaemia may also occur.

Supportive and symptomatic treatment may be indicated. Beta-blockers should be used with care because of the possibility of inducing bronchospasm in sensitive individuals. If DUORESP SPIROMAX therapy has to be withdrawn due to overdose of the formoterol component, provision of appropriate inhaled corticosteroid therapy must be considered.

Budesonide

Acute overdosage with budesonide, even in excessive doses, is not expected to be a clinical problem. When used chronically in excessive doses, systemic glucocorticosteroid effects may appear, such as hypercorticism and adrenal suppression.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergics and other drugs for obstructive airway diseases.

ATC code: R03AK07

DUORESP contains formoterol and budesonide which have different modes of action and show additive effects in terms of reduction of asthma exacerbations. The specific properties of budesonide and formoterol allow the combination to be used both as maintenance and reliever therapy, and as maintenance treatment for asthma.

Budesonide

Budesonide is a glucocorticosteroid which when inhaled has a rapid (within hours) and dose-dependent anti-inflammatory action in the airways, resulting in reduced symptoms and fewer asthma exacerbations. Inhaled budesonide has less severe adverse effects than systemic corticosteroids. The exact mechanism responsible for the anti-inflammatory effect of glucocorticosteroids is unknown.

Formoterol

Formoterol is a selective beta2-adrenergic agonist that when inhaled results in rapid and long-acting relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect is dose dependent, with an onset of effect within 1-3 minutes. The duration of effect is at least 12 hours after a single dose.

Clinical Efficacy and Safety Data

The reported clinical studies are those of the innovator reference product being compared against the respective monotherapies and alternative treatments for asthma and COPD. Bioequivalence has been demonstrated between DUORESP SPIROMAX dry powder inhaler and the innovator reference dry powder inhaler for the 200/6 and 400/12 doses. Additionally, an investigation was conducted to assess inspiratory flow rates achieved using the SPIROMAX device as this device is different to the innovator dry powder inhaler device.

Peak Inspiratory Flow rate through the SPIROMAX device

A randomised, open label placebo study was performed in children and adolescents with asthma (aged 6 -17 years), adults with asthma (18-45 years), adults with chronic obstructive pulmonary disease (COPD aged >50 years) and healthy volunteers (aged 18-45 years) to evaluate the peak inspiratory flow rate (PIFR) and other related inhalation parameters following inhalation from a SPIROMAX device (containing placebo) compared with inhalation from an already marketed multi dose dry powder inhaler device (containing placebo). The impact of enhanced training in dry powder inhalation technique on inhalation speed and volume was also assessed in these subject groups. The data from the study indicated that regardless of age and underlying disease severity, children, adolescents and adults with asthma as well as patients with COPD were able to achieve inspiratory flow rates through the SPIROMAX device that were similar to those generated through the marketed multi dose dry powder inhaler device. The mean PIFR achieved by patients with asthma or COPD was over 60 L/min, a flow rate at which both devices studied are known to deliver comparable amounts of drug to the lungs. Very few patients had PIFRs below 40 L/min; when PIFRs were less than 40 L/min there appeared to be no clustering by age or disease severity.

Clinical Efficacy for budesonide/formoterol as an anti-inflammatory reliever: anti-inflammatory reliever therapy (therapy A) and anti-inflammatory reliever plus maintenance therapy (therapy B) in asthma (see section 4.2 Dose and Method of Administration).

Overall, 20,140 asthma patients were included in 7 double-blind clinical studies, of which 7,831 were randomised to a therapy which included budesonide/formoterol as an anti-

inflammatory reliever, both with a maintenance (therapy B) and without a maintenance dosing (therapy A).

A total of 8,064 asthma patients with mild asthma were included in 2 double-blind efficacy and safety studies (SYGMA 1 and SYGMA 2 studies), of which 3,384 patients were randomised to budesonide/formoterol anti-inflammatory reliever therapy (therapy A) for 12 months. Patients were required to be uncontrolled on only short-acting inhaled bronchodilator as needed or controlled on a low dose of inhaled corticosteroids or leukotriene receptor agonist plus short-acting inhaled bronchodilator as needed.

In the SYGMA 2 study, budesonide/formoterol 200/6 used as needed in response to symptoms (anti- inflammatory reliever therapy – therapy A) was comparable to a maintenance dose of budesonide (1 inhalation of 200 micrograms/inhalation twice daily) given with as-needed short- acting beta-2-agonist in terms of the rate of severe exacerbations (Table 2). Protection against severe exacerbation was achieved with a 75% reduction in median inhaled steroid load and without requiring adherence to maintenance inhaled corticosteroids treatment. The SYGMA 1 study showed that budesonide/formoterol anti-inflammatory reliever therapy provided statistically significant and clinically meaningful reduction in the rate of annual severe exacerbation by 64% compared with as-needed use of a short-acting beta-2-agonist (Table 2). Reduction in the annual rate of moderate to severe exacerbations was consistent (60%) with that observed for severe exacerbations ([RR] 0.40, 95% CI 0.32 to 0.49, p-value <0.001).

In the SYGMA 1 study, as-needed use of budesonide/formoterol 200/6 provided superior daily asthma symptom control compared to as-needed short-acting beta-2-agonist (OR 1.14, 95% CI 1.00 to 1.30, p-value 0.046), showing a mean percentage of weeks with well-controlled asthma of 34.4% and 31.1%, respectively. Asthma symptom control was inferior for budesonide/formoterol as needed compared to a maintenance dose of budesonide (1 inhalation of 200 micrograms/inhalation twice daily) given with as-needed short-acting beta-2-agonist (OR 0.64, 2-sided 95% CI 0.57 to 0.73, lower limit of the CI ≥ 0.8 for non-inferiority), showing a mean percentage of well- controlled asthma weeks of 34.4% and 44.4%, respectively. Improvements in asthma control (as defined by ACQ5) in patients using budesonide/formoterol anti-inflammatory reliever therapy were superior to improvements in patients using a short-acting beta-2-agonist as needed (-0.15, 95% CI -0.20 to -0.11, p-value < 0.001). Improvements in asthma control were lower for budesonide/formoterol as needed compared to a maintenance dose of budesonide (1 inhalation of 200 micrograms/inhalation twice daily) given with a short-acting beta-2-agonist to be used as needed (SYGMA 1: 0.15, 95% CI 0.10 to 0.20; SYGMA 2: 0.11, 95% CI 0.07 to 0.15, both p-value < 0.001). For both comparisons, mean differences in treatments' effect upon ACQ5 are not clinically meaningful (as assessed by a difference of greater than or equal to 0.5). These results were observed in a clinical study setting with considerably higher adherence to budesonide maintenance dosing than expected in real life.

In the SYGMA studies, increases in lung function compared to baseline (mean pre-bronchodilator FEV1) were statistically significantly larger for patients on budesonide/formoterol anti- inflammatory reliever therapy compared to patients on as-needed short-acting beta-2-agonist treatment. Statistically significantly smaller increases were observed for budesonide/formoterol as needed compared to a maintenance dose of

budesonide (1 inhalation of 200 micrograms/inhalation twice daily) given with a short-acting beta-2-agonist to be used as needed. For both comparisons, mean differences in treatments' effect were small (approximately 30 to 55 mL, equating to approximately 2% of the baseline mean).

Overall, the results of the SYGMA studies show that budesonide/formoterol anti-inflammatory reliever therapy is a more effective treatment than a short-acting beta-2-agonist as needed in patients with mild asthma. In addition, these studies suggest that the as-needed use of budesonide/formoterol may be considered an alternative treatment option for patients with mild asthma who are eligible for inhaled corticosteroid treatment.

In a separate clinical programme, a total of 12,076 asthma patients were included in 5 double-blind clinical studies (4447 were randomised to budesonide/formoterol anti-inflammatory reliever plus maintenance therapy – therapy B) for 6 or 12 months. Patients were required to be symptomatic despite daily use of inhaled glucocorticosteroids. Budesonide/formoterol anti-inflammatory reliever plus maintenance therapy provided statistically significant and clinically meaningful reductions in severe exacerbations by prolonging time to first event and reducing the event rate (Table 2), as compared with all comparator treatments, including budesonide/formoterol at a higher maintenance dose (in Study 735). Symptom control, lung function and reliever use were similar compared with a higher maintenance dose of budesonide/formoterol, and all three parameters were improved compared with budesonide/formoterol at the same maintenance dose or budesonide at a 2 to 4 times higher maintenance dose.

Clinical Efficacy for the Budesonide/formoterol maintenance and reliever therapy

A total of 12076 asthma patients were included in 5 double-blind clinical studies (4447 were randomised to budesonide/formoterol maintenance and reliever therapy) for 6 or 12 months. Patients were required to be symptomatic despite daily use of inhaled glucocorticosteroids. The budesonide/formoterol maintenance and reliever therapy provided statistically significant and clinically meaningful reductions in severe exacerbations by prolonging time to first event and reducing the event rate (Table 2), as compared with all comparator treatments, including budesonide/formoterol at a higher maintenance dose (in Study 735). Symptom control, lung function and reliever use were similar compared with a higher maintenance dose of budesonide/formoterol fixed combination, and all three parameters were improved compared with budesonide/formoterol fixed combination at the same maintenance dose or budesonide at a 2 to 4 times higher maintenance dose.

Table 2 Overview of severe exacerbations in clinical studies

Study No., Age group	Treatment groups[a]	N	Severe exacerbations[b]	
			Number of events	Exacerbations /patient/year[c]
SYGMA 1 (Therapy A*), ≥ 12 years	**Budesonide/formoterol 160/4.5 as needed**	**1277**	**77**	**0.07**
	Terbutaline 0.4 mg as needed	**1277**	**188**	**0.20[d]**
	Budesonide 200 µg bd + terbutaline 0.4 mg as needed	**1282**	**89**	**0.09[e]**
SYGMA 1 (Therapy A*), ≥ 12 years	**Budesonide/formoterol 160/4.5 as needed**	2084	217	0.11
	Budesonide 200 µg bd + terbutaline 0.4 mg as needed	2083	221	0.12[f]
6-month double-blind studies				
Study 735, (Therapy B) ≥ 12 years**	**Budesonide/formoterol 160/4.5 µg bd + as needed**	**1103**	**125**	**0.23****
	Budesonide/formoterol 320/9 µg bd + terbutaline 0.4 mg as needed	1099	173	0.32
	Salmeterol/fluticasone 2x25/125 µg bd + terbutaline 0.4 mg as needed	1119	208	0.38
Study 667, (Therapy B) 12-80 years**	**Budesonide/formoterol 2 x 80/4.5 µg od + as needed**	**354**	**14**	**0.08****
	Budesonide 2 x 160 µg od + terbutaline 0.4 mg as needed	342	57	0.35
12-month double-blind studies				
Study 734, (Therapy B) ≥ 12 years**	**Budesonide/formoterol 160/4.5 µg bd + as needed**	**1107**	**194**	**0.19****
	Budesonide/formoterol 160/4.5 µg bd + formoterol 4.5 µg as needed	1137	296	0.29
	Budesonide/formoterol 160/4.5 µg bd + terbutaline 0.4 mg as needed	1138	377	0.37
Study 673, (Therapy B) 4-80 years[g]**	**Budesonide/formoterol 80/4.5 µg bd + as needed**	**922**	160	**0.19****
	Budesonide/formoterol 80/4.5 µg bd + terbutaline 0.4 mg as needed	906	330	0.40
	Budesonide 320 µg bd + terbutaline 0.4 mg as needed	925	294	0.35

Study No., Age group	Treatment groups[a]	N	Severe exacerbations[b]	
			Number of events	Exacerbations /patient/year[c]
4-11 years	**Budesonide/formoterol 80/4.5 µg od + as needed**	**118**	**11**	**0.10****
	Budesonide/formoterol 80/4.5 µg od + terbutaline 0.4 mg as needed	117	52	0.46
	Budesonide 320 µg od + terbutaline 0.4 mg as needed	106	32	0.33
Study 668, 12-80 years	**Budesonide/formoterol 160/4.5 µg od + as needed**	947	197	0.23**
	Budesonide 2 x 160 µg bd + terbutaline 0.4 mg as needed	943	349	0.42

** Reduction in exacerbation rate is statistically significant (*P* value <0.01) (for both comparisons where applicable).

[a] All doses expressed as delivered dose. Budesonide 160 µg and 320 µg (delivered doses) correspond to budesonide monoproduct 200 µg and 400 µg (metered doses), respectively.

[b] Defined as hospitalisation/emergency room treatment or treatment with oral steroids due to asthma (and for children, also an increase in inhaled steroid dose or additional asthma treatment).

[c] Data normalised to 12 months for studies 735, 667, 734 and 673.

[d] Reduction in exacerbation rate is statistically significant (p-value <0.001) for the comparison of budesonide/formoterol as needed vs Terbutaline as needed.

[e] Reduction in exacerbation rate is not statistically significantly different (p-value 0.279) when comparing budesonide/formoterol as needed vs Budesonide 200 µg bd + terbutaline 0.4 mg as needed in SYGMA 1.

[f] Budesonide/formoterol as needed was non-inferior to Budesonide 200 µg bd + terbutaline 0.4 mg as needed in reducing the severe exacerbation rate in SYGMA 2. The upper limit (1.16) of the 95% CI for the rate ratio (RR) was below the pre-specified non-inferiority limit (1.20).
[g] Includes children ages 4 to 11 that received half the maintenance dose, who are also presented separately.

Analysis of time to first severe exacerbation in the SYGMA 1 study showed that the likelihood of experiencing a severe exacerbation was statistically significantly higher for the as-needed use of a short-acting beta-2-agonist compared to the as-needed use of budesonide/formoterol (anti-inflammatory reliever therapy - therapy A) over the 1 year treatment period (see Figure 1a), with a risk reduction of 56% ([HR] 0.44, 95% CI: 0.33-0.58, p-value < 0.001). There were no differences in the probability of experiencing a severe exacerbation between anti-inflammatory reliever therapy (therapy A) and a therapy including

a inhalation of 200 micrograms/inhalation twice daily) and a short-acting beta-2-agonist used as needed (see Figure 1a and 1b).

Figure 1a Time to first severe asthma exacerbation in SYGMA 1 study

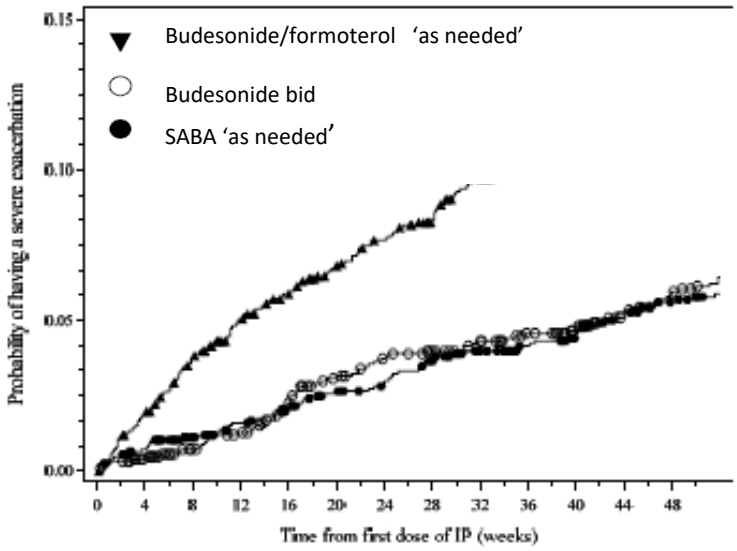
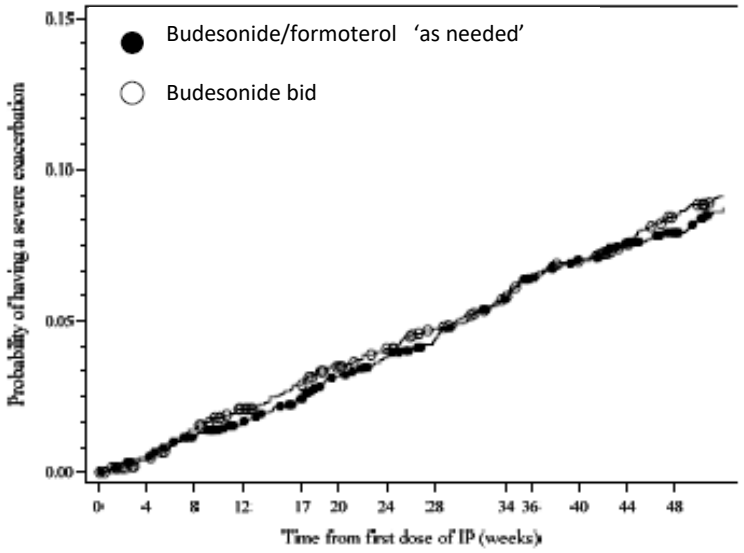
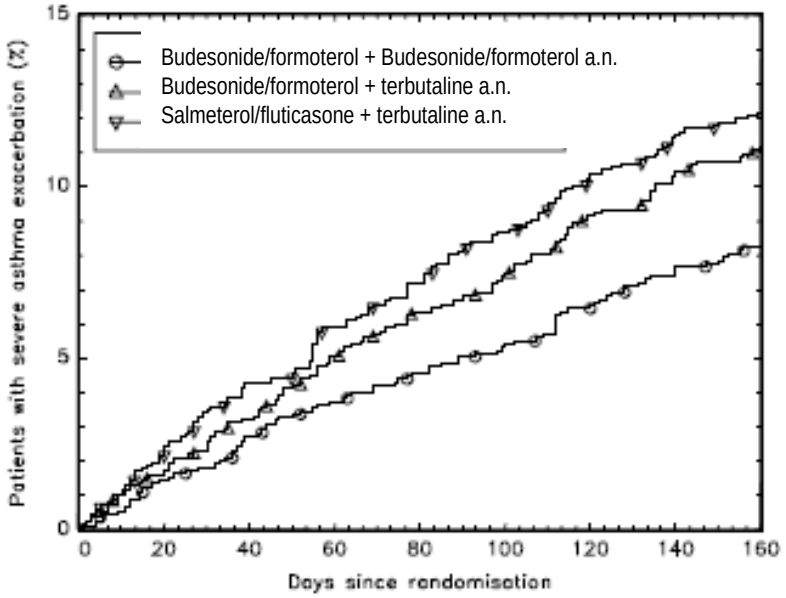


Figure 1b Time to first severe asthma exacerbation in SYGMA 2 study



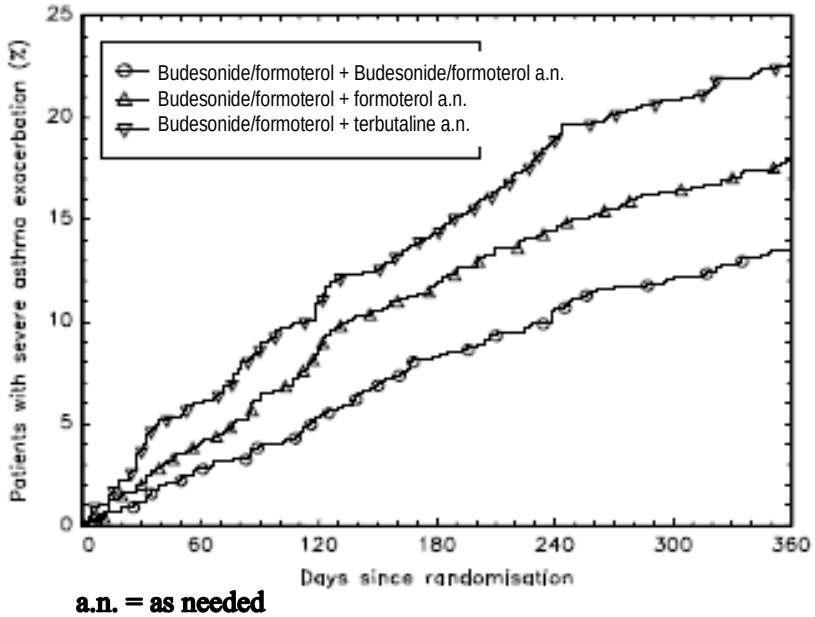
In Study 735, the budesonide/formoterol anti-inflammatory reliever plus maintenance therapy (therapy B) significantly prolonged the time to the first exacerbation (see Figure 2a) compared to the other treatment groups. The rate of exacerbations was reduced by 28% compared to twice the maintenance dose of budesonide/formoterol fixed combination with terbutaline as reliever. Lung function, symptom control, and reliever use were similar in all treatment groups.

Figure 2a Time to first severe asthma exacerbation in study 735



a.n. = as needed

Figure 1b Time to first severe asthma exacerbation in study 734



a.n. = as needed

In Study 734, the budesonide/formoterol reliever plus therapy (therapy B) prolonged the time to the first exacerbation compared to budesonide/formoterol at the same maintenance dose with either formoterol or terbutaline as reliever (see Figure 2b). The rate of exacerbations was reduced by 33% and 48%, respectively. Symptoms and reliever use were reduced and lung function improved, compared with both comparator treatments.

In Studies 673, 668 and 667, the budesonide/formoterol reliever plus maintenance therapy (therapy B) prolonged the time to the first exacerbation compared to budesonide/formoterol at the same maintenance dose with terbutaline as reliever and compared to a 2- to 4-fold higher maintenance dose of budesonide with terbutaline as reliever. Across the 3 studies, the rate of exacerbations was reduced by 45-76%. Symptoms and reliever use were reduced and lung function improved compared with all other treatments. For children (118 randomised to the budesonide/formoterol reliever plus maintenance therapy in study 673), the exacerbation rate was reduced by 70-79%.

In the 5 long-term studies, patients (adults and adolescents) receiving the budesonide/formoterol anti-inflammatory reliever plus maintenance therapy (therapy B) were allowed 12 inhalations per day (maintenance and as needed) without being reassessed. On average, no reliever inhalation was used on 57% of treatment days and 0-2 reliever inhalations on 87% of treatment days. There was no sign of development of tolerance over time.

In two studies separate studies with patients seeking medical attention due to acute asthma symptoms, budesonide/formoterol provided rapid and effective relief of bronchoconstriction similar to salbutamol and formoterol.

Clinical Efficacy in asthma for the budesonide/formoterol maintenance therapy (therapy C)
Clinical studies have shown that the addition of formoterol to budesonide improved asthma symptoms and lung function, and reduced exacerbations. The effect on lung function of budesonide/formoterol fixed combination, given as a maintenance dose only, was equal to that of budesonide and formoterol in separate inhalers in adults and exceeded that of budesonide alone in adults and children. All treatment arms used a short acting beta-2-agonist as needed. There was no sign of attenuation of the anti-asthmatic effect over time.

Clinical Efficacy in Chronic Obstructive Pulmonary Disease (COPD)
In two 12-month studies in patients with COPD, budesonide/formoterol combination was superior to placebo, formoterol and budesonide regarding lung function, and showed a significant reduction in the exacerbation rate compared to formoterol and placebo. Thus, the contribution of both budesonide and formoterol to the effect of budesonide/formoterol combination was demonstrated. Budesonide/formoterol combination was also superior to placebo regarding symptoms and quality of life. The treatment was well tolerated.

5.2 Pharmacokinetic properties

Absorption

The fixed-dose combination of budesonide and formoterol, and the corresponding monoproducts have been shown to be bioequivalent with regard to systemic exposure of budesonide and formoterol, respectively.

There was no evidence of pharmacokinetic interactions between budesonide and formoterol.

Pharmacokinetic parameters, for the respective substances were comparable after the administration of budesonide and formoterol as monoproducts or as the fixed-dose combination.

Inhaled budesonide is rapidly absorbed and the maximum plasma concentration is reached within 30 minutes after inhalation.

In studies, mean lung deposition of budesonide after inhalation of budesonide via powder for inhalation device, ranged from 32 to 44% of the delivered dose. The systemic bioavailability is approximately 49% of the delivered dose.

Inhaled formoterol is rapidly absorbed and the maximum plasma concentration is reached within 10 minutes after inhalation. In studies, the mean lung deposition of formoterol after inhalation of formoterol via powder for inhalation device, ranged from 28-49% of the delivered dose. The systemic availability is about 61% of the delivered dose.

Distribution and Metabolism

Plasma protein binding is approximately 50% for formoterol and 90% for budesonide. Volume of distribution is about 4 L/kg for formoterol and 3 L/kg for budesonide. Formoterol is inactivated via conjugation reactions (active O-demethylated and deformylated metabolites are formed, but they are seen mainly as inactivated conjugates). Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxy-budesonide and 16α-hydroxy-prednisolone, is less than 1% of that of budesonide. There are no indications of any metabolic interactions or any displacement reactions between formoterol and budesonide.

Elimination

The major part of a dose of formoterol is eliminated by metabolism in the liver followed by renal excretion. After inhalation, 8-13% of the delivered dose of formoterol is excreted unmetabolised in the urine. Formoterol has a high systemic clearance (approximately 1.4 L/min) and the terminal elimination half-life averages 17 hours.

Budesonide is eliminated via metabolism mainly catalysed by the enzyme CYP3A4. The metabolites of budesonide are excreted in urine as such or in conjugated form. Only negligible amounts of unchanged budesonide have been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 L/min) and the plasma elimination half-life after intravenous dosing averages 4 hours.

Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 year old asthmatic children. Per kg body weight children have a clearance which is approximately 50% greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2.3

hours in asthmatic children. The pharmacokinetics of formoterol in children has not been studied.

The pharmacokinetics of budesonide or formoterol in elderly and patients with renal failure is unknown. The exposure of budesonide and formoterol may be increased in patients with liver disease.

DUORESP SPIROMAX pharmacokinetic profile

In pharmacokinetic studies with and without a charcoal blockage, DUORESP SPIROMAX was evaluated by comparing it against the innovator fixed-dose combination inhalation product containing the same active substances. Budesonide and formoterol have been shown to be equivalent in both pulmonary and systemic deposition for the 200/6 and 400/12 doses.

5.3 Preclinical safety data

The toxicity observed in animal studies with budesonide and formoterol was similar whether budesonide or formoterol were given in combination or separately. The effects were associated with pharmacological actions and dose dependent.
In animal reproduction studies, corticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not seem to be relevant in humans at the recommended doses (see Section 4.6 - Fertility, Pregnancy and Lactation). Animal reproduction studies with formoterol have shown a somewhat reduced fertility in male rats at high systemic exposure and implantation losses as well as decreased early postnatal survival and birth weight at considerably higher systemic exposures than those reached during clinical use. However, these animal experimental results do not seem to be relevant to man.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C. Replace cap firmly after use.

Use the product within 6 months of removing from foil wrapping.

6.5 Nature and contents of container

DuoResp Spiromax is available as a multidose inspiratory flow driven, metered dose dry powder inhaler (Spiromax). To avoid confusion, DuoResp Spiromax is labelled as the metered dose of the corresponding monotherapy products budesonide and formoterol dry

powders for inhalation. The monotherapy products are also labelled as metered doses. The following table gives the corresponding dose delivered to the patient.

Table 3

Budesonide/ Formoterol	Metered dose* (µg)		Corresponding dose deliver to patient (µg)	
	Budesonide	Formoterol	Budesonide	Formoterol
200 / 6	200	6	160	4.5
400 / 12	400	12	320	9

DuoResp Spiromax 200/6 is registered* as a 120 dose inhaler in packs of 1, 2 or 3.

DuoResp Spiromax 400/12 is registered* as a 60 dose inhaler in packs of 1, 2 or 3.

*Not all pack sizes are commercially available.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MEDICINE SCHEDULE

Prescription medicine.

8 SPONSOR

Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9 DATE OF FIRST APPROVAL

30 May 2019

10 DATE OF REVISION OF THE TEXT

8 December 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
Various	Editorial corrections
4.2	Update to include adolescents in dosage instructions for Asthma
4.4	Pneumonia in COPD patients subsection amended in line with recent data
4.6	Update to figures based on latest data
4.8	New ADR (pneumonia) included in Table 1